CLINICAL STUDY

Role of Beta-Blockers in Prevention of Hepatopulmonary Syndrome in Chronic Liver Disease: An Observation

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ABSTRACT

Aim: Study was initiated to study the presence of hepatopulmonary syndrome (HPS) in chronic liver disease patients, and role of beta-blockers in its occurrence. **Methods:** Patients admitted in Dept. of Medicine and patients attending the Medicine OPD were examined and investigated for presence of HPS irrespective of its typical clinical features as explained in the literature. Patients having ascites or pleural effusion were managed by means of paracentesis and pleural tap first and then included in the study. Patients having any other primary pulmonary disease like bronchial asthma or chronic obstructive pulmonary disease were excluded from the study. Arterial blood gas analysis and contrast-enhanced echocardiography was done to confirm presence of arterial hypoxemia and pulmonary shunt, the diagnostic criteria. **Results:** During 1 year study, total 125 patients were enrolled in the study after appropriate selection criteria. Twenty-eight out of 125 patients were not taking propranolol. Propranolol is contraindicated in these patients for one or two reasons. Four out of these 28 patients developed HPS. One out of 97 patients who were on propranolol developed HPS. Total 5 patients were confirmed having HPS. The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$. **Conclusion:** Patients of cirrhosis with portal hypertension on treatment with propranolol were having significantly lower chances of development of HPS then those without propranolol. Propranolol may have preventive role for development of HPS.

Keywords: Hepatopulmonary syndrome, beta-blockers, chronic liver disease

Hepatopulmonary syndrome (HPS) and porto-pulmonary syndrome are two rare, but fatal extrahepatic complications of chronic liver disease and portal hypertension. Till date, no definitive treatment options are available for managing these complications. Few studies claim liver transplantation as the definitive treatment. Flückiger in 1884 for the first time recognized this clinical entity as complication of liver cirrhosis. Liver disease, with presence of arterial hypoxemia evident on arterial blood gas (ABG) analysis, and intrapulmonary vascular shunt as evident on contrast-enhanced echocardiography or use of technetium-99m–labeled macroaggregated albumin for lung scanning with quantitative brain uptake makes the triad of HPS. Clinical presentations are nonspecific and may include dyspnea on exertion or rest, presence of spider angiomas, clubbing, cyanosis, and severe arterial hypoxemia. This study was conducted with the aim to evaluate patients of chronic liver disease for presence of HPS. Diagnostic criteria for HPS are given in Table 1[1]. Retrospective data regarding diagnosis and treatment were collected and evaluated for treatment given so far for management of cirrhosis.

METHODS

One hundred twenty-five patients with liver disease of varied etiologies were enrolled in the study after

Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome[1]

Oxygenation defect	Partial pressure of oxygen <80 mmHg or alveolar-arterial oxygen gradient ≥15 mmHg, while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis

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appropriate selection criteria. Patients with any evidence of primary respiratory or cardiac disease were excluded. Cirrhosis and portal hypertension was confirmed by history, clinical examination, pathological investigations and radiology.

Patients were further evaluated for presence of platypnea, cyanosis, clubbing, and angiomas; the typical associations of HPS. Irrespective of the grade of cirrhosis and presence of signs and symptoms all selected patients were evaluated for pulmonary shunt. For this, a transthoracic contrast echocardiography was done using agitated saline. Visibility of micro-bubbles in the left atrium between 3 to 6 cardiac cycles after they were seen in right-atrium indicated micro-bubble passage through an abnormally dilated vascular bed. A due consent was taken from patients for this examination.

An ABG analysis was done in these patients. ABG was done in both resting supine position and in sitting upright position after 5 minutes. As per the diagnostic criteria in Table 1, cut-off value for considering HPS were resting PO_2 <80 mmHg and/or ΔPO_2, i.e., PO_2 (A-a) ≥15 mmHg. We used resting PO_2 in our study. Using these criteria 5 patients were diagnosed to have HPS. Out of 125 patients, 97 were using propranolol, whereas 28 were not using propranolol as it was contraindicated in them due to one or more side effects in them. Propranolol is a drug used in portal hypertension as prophylaxis for secondary variceal bleeding. Four out of 28 developed HPS, whereas only 1 out of 97 developed HPS. The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$.

RESULTS

Out of 125 patients, 5 patients fulfilled the diagnostic criteria for presence of HPS. The mean age of patients was 52.6 years with standard deviation (SD) = 10.6. Eighty-four were male and 41 were females. Cause of chronic liver disease were alcoholic liver disease 56 (44.8%), chronic hepatitis B 38 (30.4%), chronic hepatitis C 14 (11.2%), noncirrhotic portal fibrosis 5 (4.0%); others and undetermined causes 12 (9.6%) (Table 2). Others included one case of autoimmune hepatitis. On the basis of examination and investigation, patients were categorized into Child's grade: A = 12, B = 20, and C = 93. On retrospective evaluation of medical records, it was found that 28 out of 125 patients were not taking propranolol or any other beta-blocker. They all had one or two contraindications for using beta-blocker. Beta-blockers are among preferred drugs used to reduce portal hypertension. Patients were categorized further in Group A (beta-blocker using group) n = 97, and Group B (beta-blocker contraindicated group) n = 28. In Group A, 1 out of 97 was diagnosed to have HPS. In Group B, 4 out of 28 patients were diagnosed to have HPS (Table 3).

Table 2. Clinical Characteristics of 125 Study Patients

Parameters	No. of patients
Sex	
Male	84
Female	41
Clinical features	
Platypnea	5
Cyanosis	12
Clubbing	42
Angiomas	3
Causes of CLD	
Alcohol	56
Hepatitis B	38
Hepatitis C	14
NCPF	5
Others	12
Reason for beta-blocker contraindications	21
Sinus bradycardia	18
Postural hypotension	2
Diabetes	3
Prolonged PR interval	

CLD = Chronic liver disease; NCPF = Noncirrhotic portal fibrosis.

Table 3. Characteristics of 5 Patients with HPS

	No. of patients
Sex	
Male	4
Female	1
Clinical features	
Platypnea	3
Cyanosis	5
Clubbing	5
Angiomas	0
Mean PaO_2	**78%**

The Fisher's exact test statistic value is 0.008887. The result is significant at $p < 0.01$. Causes of contraindications for beta-blocker use were sinus bradycardia, clinical postural hypotension, diabetes, prolonged PR interval.

DISCUSSION

Cirrhosis leads to a hyperdynamic state of circulation especially in presence of acute or chronic hepatocellular failure[2]. Peripheral vasodilatation and reduced peripheral vascular resistance manifests with peripheral flushing, erythema, decreased blood pressure, and bounding pulse. Cardiac output is increased to compensate for above. The numerous functionally inactive arteriovenous fistulas open up due to this profound vasodilatation. HPS is manifestation of similar mechanism in liver cirrhosis, which develops when the pulmonary venous shunt is at its extreme[3]. Cyanosis and reduced oxygen saturation is a frequent finding in decompensated cirrhosis[4]. Various medications are tried in HPS with variable effectiveness but most do not seems to be effective in its reversal. Pentoxyphyllin[5] and methylene blue[6] till date are found effective up to a certain extent in HPS reversal.

Beta-blockers are among the preferred drugs for patients with portal hypertension. They are given in titrated doses to prevent primary and secondary bleeding from esophageal varices. Beta-blockers were clearly declared ineffective in management of HPS[7]. Still, there are few hopes in theory favoring them to use in HPS. A case report published in 1994 by Saunders et al, in which a patient improved from HPS proved by serial exercise testing[8]. This patient was on beta-blocker for some time after which he showed signs of improvement. Although author itself was not able to describe the role of beta-blocker in improvement from HPS still comparing the data from our study with this case may open the new ways of thoughts in using beta-blockers as prophylaxis or may be for treatment of HPS.

REFERENCES

1. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome - a liver-induced lung vascular disorder. N Engl J Med. 2008;358(22):2378-87.
2. Murray JF, Dawson AM, Sherlock S. Circulatory changes in chronic liver disease. Am J Med. 1958;24(3):358-67.
3. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB; ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-Hepatic vascular Disorders (PHD). Eur Respir J. 2004;24(5):861-80.
4. Rodman T, Sobel M, Close HP. Arterial oxygen unsaturation and the ventilation-perfusion defect of Laennec's cirrhosis. N Engl J Med. 1960;263:73-7.
5. Sztrymf B, Rabiller A, Nunes H, Savale L, Lebrec D, Le Pape A, et al. Prevention of hepatopulmonary syndrome and hyperdynamic state by pentoxifylline in cirrhotic rats. Eur Respir J. 2004;23(5):752-8.
6. Schenk P, Madl C, Rezaie-Majd S, Lehr S, Müller C. Methylene blue improves the hepatopulmonary syndrome. Ann Intern Med. 2000;133(9):701-6.
7. Rodríquez-Roisin R, Krowka MJ, Hervé P, Fallon MB; ERS (European Respiratory Society) Task Force-PHD Scientific Committee. Highlights of the ERS Task Force on pulmonary-hepatic vascular disorders (PHD). J Hepatol. 2005;42(6):924-7.
8. Saunders KB, Fernando SS, Dalton HR, Joseph A. Spontaneous improvement in a patient with the hepatopulmonary syndrome assessed by serial exercise tests. Thorax. 1994;49(7):725-7.